Antibiotic Pressure is a Major Risk Factor for Rectal Colonization by Multidrug-resistant *Pseudomonas aeruginosa* in Critically ill Patients.

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The intestinal reservoir is central to the epidemiology of *Pseudomonas aeruginosa* (PA), but the dynamics of intestinal colonization by different phenotypes is poorly described. To determine the impact of antimicrobial exposure on intestinal colonization by multidrug-resistant (MDR) and extensively drug-resistant (XDR) PA, we screened intensive care unit (ICU) patients for rectal colonization on admission and at weekly intervals. During an 18 months study period, 414 ICU patients were enrolled, of whom, 179 (43%) were colonized; 112 (63%) were identified at ICU admission and 67 (37%) during ICU stay. At 10 days after ICU admission, the probabilities of PA carriage were 44%, 24%, and 24% for non-MDR, MDR-non-XDR, and XDR PA respectively (Log Rank=0.02). Pulsed-gel electrophoresis showed 10 pairs of non-MDR PA and subsequent MDR-non-XDR strains isolated from the same patients to be clonally identical, and another 13 pairs (8 MDR-non-XDR and 5 XDR) to be unrelated. There was one specific clone between the 8 MDR-non-XDR strains and an identical genotype in the 5 XDR isolates. Cox regression analysis identified MDR PA acquisition as associated with underlying disease severity (adjusted hazard ratio [aHR], 1.97; 95%CI 1.22-3.18; p = 0.006), and prior use of fluoroquinolones (aHR, 1.02; 95%CI 1.00-1.04; p = 0.039), group 2 carbapenems (aHR, 1.03; 95%CI 1.00-1.07; p = 0.041), and ertapenem (aHR, 1.08; 95%CI 1.02-1.14; p = 0.004). The epidemiology of MDR PA is complex and different clusters may coexist. Interestingly, ertapenem was found to be associated with the emergence of MDR isolates.
*Pseudomonas aeruginosa* (PA) is one of the most common nosocomial pathogens worldwide, and continuously evolving resistance to multiple antimicrobial agents has become a significant health problem. Control of multidrug-resistant (MDR) PA in the intensive care units (ICUs) is an important method of preserving the limited number of drugs available for treating PA infections. However, this control is difficult to achieve because the path of emergence and dissemination of MDR PA is not fully understood. As an endogenous source of endemic or epidemic infection with Gram-negative bacilli (GNB), the intestinal reservoir is central to the epidemiology of PA because prior rectal colonization is typically present in most patients developing GNB infections (1).

Several studies have demonstrated that prior antimicrobial drug exposure is also a strong risk factor for colonization with a drug-resistant pathogen (2,3). In fact, we have previously reported an association between carbapenem and fluoroquinolone consumption with the probability of colonization by carbapenem resistant PA in ICU patients (4).

Over recent years, important changes have occurred in the epidemiology of MDR PA. First, in addition to the characteristics polyclonal pattern of endogenous PA, a newly identified epidemic clonal pattern has been described during MDR PA outbreak (5). Second, several reports have provided strong evidence for the existence of MDR PA high risk clones (6), with biological parameters that may explain the success of these specific clones (7). Finally, a recent consensus document (8) proposed a set of MDR definitions in pathogenic bacteria that may improve the comparability of surveillance data. To our knowledge, no study has applied these new definitions to the
epidemiological behavior of MDR PA, and extensively drug-resistant (XDR) PA. In addition, the impact of ertapenem use over time is an issue of recent controversy (9).

For all these reasons we decided to analyze the influence of antimicrobial use in intestinal PA colonization in ICU patients. Additionally, we assessed the temporal changes and the dynamic characteristics of intestinal colonization by different PA phenotypes in ICU patients after starting antibiotic therapy. This study aimed to compare the probability of intestinal colonization by non-MDR PA and MDR PA, and to assess the relationship between the duration of antibiotic therapy exposure and intestinal colonization with PA.

**MATERIAL AND METHODS**

We conducted a prospective cohort study of patients admitted to a medical-surgical ICU at the Hospital Universitari de Bellvitge between January 2012 and June 2013. All samples and examinations were performed as part of the standard care procedures for epidemiological control in this population. The local ethic committee of our hospital approved the study, and patients or family provided informed consent.

Study design. We conducted an active surveillance program with ICU patients. Weekly rectal swab samples were obtained immediately on admission, to detect digestive tract carriage of PA, and between ICU admission and discharge. To study patients at risk for digestive tract carriage during their ICU stay, all patients admitted to the unit for more than 48 hours were included. We collected the following information for each patient: demographic data including, sex, age, hospital admission date, ICU admission date, and ICU discharge date;
and severity of acute illness on ICU admission using the simplified acute physiologic score (SAPS) (10), and the Charlson Comorbidity index (11).

**Definitions.** We defined ICU admission carriers as patients with PA-positive culture samples at ICU admission. We considered ICU-acquired carriers as patients with PA-negative culture samples at ICU admission, and who developed a PA-positive culture either during ICU admission or at ICU discharge. In addition, new ICU acquisition was considered if the PA phenotype isolated in a rectal sample differed to that of a previous isolate.

The phenotype stratification of PA isolates was made in accordance with recent standard definitions (8). MDR PA was defined as a strain non-susceptible to ≥1 agent in ≥3 antipseudomonal antimicrobial categories. XDR PA was defined as non-susceptible to ≥1 agent in all but ≤2 antipseudomonal antimicrobial categories; thus, XDR PA isolates were included as MDR PA. To study the specific epidemiology of XDR PA, MDR PA isolates were distributed as follows: XDR PA as defined above, and MDR-non-XDR PA defined as PA strains non-susceptible to ≥1 agent in ≥3 antipseudomonal antimicrobial categories, but susceptible in at least >2 antipseudomonal antimicrobial classes. All other PA isolates, including those non-susceptible to ≥1 agent in <3 antimicrobial categories, were considered non-MDR PA. Thus, three phenotypes of PA isolates were considered: non-MDR, MDR-non-XDR and XDR. Only the first PA isolate of a specific phenotype was taken into account for each patient. Isolates of different phenotypes in the same patient were considered to be differentiated colonization episodes.

The length of exposure to antibiotic therapy for patients colonized by PA was defined by the number of days of therapy, with different groups of
antibiotics, that a patient had received in the three months prior to hospital admission, and until PA rectal colonization. The groups of antibiotics analyzed were: non antipseudomonal penicillins (penicillin G, ampicillin, amoxicillin-clavulanic acid, cloxacillin); antipseudomonal penicillin (piperacillin-tazobactam); non antipseudomonal cephalosporins; antipseudomonal cephalosporins (ceftazidime, cefepime); aztreonam; aminoglycosides; glyco-lipopeptides; fluoroquinolones; group 2 antipseudomonal carbapenems (meropenem and imipenem); and ertapenem (group 1 carbapenem). For new ICU-acquired carrier status, the length of exposure to antibiotic therapy was calculated to the date of the new positive sample. For patients not colonized by PA, the length of exposure was defined as the number of days of prior antibiotic consumption to the date of withdrawal or ICU discharge.

**Microbiological studies.** We identified PA strains and tested for antimicrobial susceptibility using a MicroScan® automated microdilution system with CN1S and CO1S panels (Dade International, West Sacramento, California). The Clinical and Laboratory Standards Institute criteria (12) were used to define susceptibility or resistance to these antimicrobial agents. Pulsed-field gel electrophoresis (PFGE), as described previously (13), was used to determine relatedness for patients who acquired intestinal colonization PA and who subsequently acquired different phenotypes of PA. DNA restriction patterns generated by PFGE, using SpeI (New England Biolabs, Izasa, Spain) were interpreted according to the criteria established by Tenover et al.(14). We selected 23 pairs of susceptible and multiresistant strains from 23 patients, with each isolated pair originating from the same patient. This resulted in 18 paired samples of non-MDR PA and MDR-non-XDR PA, and 5 paired samples of non-
MDR PA and XDR PA. In addition, a PFGE analysis was performed in all MDR PA isolates (37 MDR-non-XDR and 46 XDR phenotypes strains). Multilocus sequence typing (MLST) as previously described (15) *P. aeruginosa* MLST database (http://pubmlst.org/paeruginosa) was used to assign sequence types (16) in one representative isolate from each of the two major clones (5,17).

**Statistical analysis.** Quantitative variables were tested for normal distribution and compared by the two-tailed *t* test or Mann-Whitney *U* test. The chi-square test or Fisher’s exact test were used to compare categorical variables. Variables with a *p* < 0.05 were considered statistically significant.

Carriers were defined as those patients with at least one PA positive rectal test result. Only the first PA isolate of a specific phenotype in each patient was included in the analysis (non MDR, MDR-non-XDR, and XDR), and they were considered different colonization episodes in the same patient. Time at risk (in days) for ICU acquisition carriers and new ICU acquisition carriers was defined as the time elapsed from ICU admission to PA isolation for colonized patients; for non-colonized patients we used the length of ICU stay.

The probability of PA carriage in the digestive tract was calculated using the Kaplan-Meier method: the outcome evaluated was PA colonization, using the date of ICU admission as time zero. Patients were monitored to ICU discharge. Only patients with a negative baseline sample at ICU admission were included in this analysis.

To assess the risk factors for MDR PA, we included all first episodes of PA colonization (according to phenotype stratification) and all non-colonized patients. To control for confounding, multivariate analysis was performed by Cox regression, using time to colonization as the dependent variable and MDR...
PA (MDR-non-XDR and XDR) colonization as the explanatory variable of interest. In the crude analysis, variables associated with exposure were candidates for multivariate analysis with if $p < 0.20$. Data were analyzed using SPSS statistical software package (version 15.0, SPSS Institute Inc, Chicago, Illinois).

RESULTS

Epidemiological characteristics. Over a period of 18 months, a cohort of 414 patients had culture samples obtained on ICU admission, with 936 rectal swabs being taken in total. Of these, 206 (50%) were screened once, while 208 (50%) had at least 2 swabs (range, 2 to 12 swabs). During their ICU stay, 179 (43%) had a PA-positive rectal sample (112 [63%] at ICU admission and 67 [37%] during ICU admission), while 235 (57%) had no evidence of colonization. Among the 179 carriers, 143 (80%) were colonized by a single resistance phenotype at ICU discharge, and 34 (20%) were colonized by different PA resistance phenotypes. The key epidemiological characteristics of patients included in the study are illustrated in Table 1.

The prevalence of PA colonization at ICU admission was 27% (112/414 patients): 89 (22%) for non-MDR PA, 6 (1%) for MDR-non-XDR PA and 17 (4%) for XDR PA. In addition, the prevalence of ICU-acquired PA colonization was 22% (67/302 patients): 43 (14%) for non-MDR, 11 (4%) for MDR-non-XDR, and 13 (4%) for XDR. Finally, among the PA colonized patients, 36 new carrier episodes were observed in 34 patients (8%) during their ICU stay (Figure 1). Thus, the total number of PA episodes was 215; 132 non-MDR and 83 MDR (37 MDR-non-XDR and 46 XDR) episodes.
Microbiological and genotypic analysis. Among the 37 MDR-non-XDR isolates analyzed, 13 were polyclonal, 19 had identical genotypes to previously described isolates (17), and were identified as ST111 clone; the remaining 5 had clonal relatedness by PFGE suggesting the occurrence of another cluster. In addition, XDR PA isolates were comparable with those of the predominant endemic clone in our hospital (5) and belonged to ST175. Identical susceptibility patterns were observed in all XDR PA strains; only amikacin and colistin retained activity in the XDR phenotype.

PFGE analysis of 18 pairs of non-MDR isolated from the same patients, were clonally identical in 10 pairs (56%) of subsequent MDR-non-XDR strains. The remaining 8 pairs (44%) were unrelated to the non-MDR PA strain by PFGE; additionally, all these 8 MDR-non-XDR strains showed clonal relatedness. In the remaining pairs, 5 non-MDR and subsequent XDR had isolates with PFGE patterns that were unrelated to prior PA isolates, but similar to those obtained from other patients (Table 2). These data confirmed clonal dissemination of both MDR-non-XDR and XDR-PA isolates in the ICU (5,17).

The dynamics of intestinal PA colonization. The unadjusted probabilities of PA carriage were analyzed among the 302 non-carriers identified at ICU admission. The mean of ICU stay for 235 non-colonized patients was 10.8±9.2 days versus 15.6±10.5 days for 67 colonized patients (p=0.001). Of these colonized patients, we identified 97 episodes: 67 initial episodes of ICU-acquired colonization and 30 subsequent new carrier episodes (Figure 1). At 10 days after ICU admission, the probabilities of PA carriage were 44%, 24%, and 24% for non-MDR, MDR-non-XDR, and XDR-PA respectively (log Rank, p = 0.02; Figure 2). Although the epidemic nature of a MDR-PA...
strain could promote spread and facilitates more rapid exogenous PA colonization, non-statistically significant differences existed in digestive tract carriage of polyclonal and clonal MDR-non-XDR PA (log Rank, p = 0.37).

Of note, among the 235 non-colonized patients, 30 (13%) with a median of ICU stay of 25 days (interquartile range [IQR], 21.75-37.25) and a median antibiotics duration of 23.5 days (IQR, 16.75-33.25) remained non-colonized during the ICU stay.

**Risk factors for MDR-PA carriage.** In total, 450 patient episodes were included (Figure 1): 235 non-colonized, 132 colonized with non-MDR PA, and 83 colonized with MDR PA (37 MDR-non-XDR and 46 XDR). We tried to define the patients at risk of acquiring intestinal colonization with MDR PA (MDR-non-XDR and XDR) intestinal colonization. The demographic characteristics and variables examined as possible risk factors are displayed in Table 3. A Cox regression model was adjusted for underlying condition severity, acute illness severity at ICU admission, and duration of prior fluoroquinolone, group 2 carbapenem, ertapenem, colistin, and piperacillin-tazobactam consumption as input variables. The model identified underlying condition severity (aHR, 1.97; 95%CI 1.22-3.18; p = 0.006), and prior fluoroquinolone (aHR, 1.02; 95%CI 1.00-1.04; p = 0.039), group 2 carbapenem (aHR, 1.03; 95%CI 1.00-1.07; p = 0.041), and ertapenem (aHR, 1.08; 95%CI 1.02-1.14; p = 0.004) consumption as independently associated with MDR PA intestinal colonization.

Analysis was performed in 37 episodes of MDR-non-XDR PA colonization episodes (13 polyclonal and 24 clonal isolates) based on the different molecular epidemiology and behavior of polyclonal and clonal strains. Cox regression identified prior ertapenem use (aHR, 1.10; 95%CI 1.01-1.19; p
0.026) as the only independent variable associated with the risk of clonal versus polyclonal MDR-non-XDR intestinal colonization (Table 4).

**DISCUSSION**

In this study, we undertook active surveillance of intestinal PA colonization in ICU patients over an 18-month period. Overall, 936 samples rectal swab were obtained from 414 patients, of which 8% were newly colonized by different PA phenotypes. There were significant differences in patient age, prior hospitalization and acute illness severity, but not prior antibiotic use, between colonized and non-colonized patients at ICU admission. Research into the molecular epidemiology revealed that XDR PA phenotypes had identical genotypes, whereas 65% of MDR non-XDR isolates presented two concomitant clusters. Furthermore, MLST study showed that the two major MDR clusters belonged to the ST 175 and ST 111 high-risk clones (5,17).

We conducted an extensive evaluation of how drug resistance levels differed at the time of intestinal colonization. We found differences in colonization dynamics, with intestinal colonization occurring more prematurely for non-MDR PA isolates. Consequently, strains exhibiting high resistance levels to antimicrobials have delayed intestinal colonization due to the time required for selective pressure to facilitate the emergence of new resistant mutants or for preexisting subpopulations of resistant organisms to emerge. In fact, molecular analysis of paired non-MDR and MDR-non-XDR PA isolates, showed that genetically identical isolates occurred in about 56% of the strains studied, due to the development of resistance in patients exposed to antibiotics. In parallel, antibiotic pressure appeared to provide a selective growth advantage...
for MDR organisms in the remaining pair isolates (44%), which had different
genotypic patterns.

In addition, the observation that similar PA genotypes colonized several
ICU patients strongly suggests cross-colonization. The presumed route of
colonization in MDR-non-XDR and XDR epidemic strains of PA could initially be
exogenous, and may occur more early than intestinal colonization.

Unfortunately, the only surveillance samples in this study were by rectal swab;
no other patient or environmental cultures were performed. Thus, rectal cultures
may not be adequate to quantify the initial colonization of patients with clonal
strains, despite epidemiological findings suggesting that patients provide a
reservoir for further environmental contamination and cross-transmission (5).

Interestingly, 13% of the patients were not colonized during prolonged
ICU stays despite high antimicrobial selection pressures. It is possible that our
detection methods for PA were insufficiently sensitive, allowing cases of rectal
colonization to be missed. However, it is equally plausible that some unknown
non-antimicrobial-related host factors may have increased the level of
colonization resistance in some patients (18).

We studied antimicrobial use and the extent of exposure before study
inclusion. It is important to know the duration of exposure to understand the
relationship between antibiotic resistance and microorganism. The present
study provides data concerning the impact of the duration of antimicrobial use
on their ability to promote digestive tract colonization with MDR PA (2,3). After
multivariate analysis, the only agents that remained significantly associated with
the MDR-PA isolation were the fluoroquinolones, and the carbapenems (both
ertapenem and group 2 carbapenems).
As expected, underlying disease severity and prior fluoroquinolone and carbapenem consumption were associated with MDR PA acquisition. Exposure to group 2 carbapenems and the fluoroquinolones are known to be associated with the development of PA infection with wider resistance profiles. Previous studies on digestive colonization in ICU patients have shown that carbapenem exposure was associated with the acquisition of carbapenem-resistant PA, with odds ratios ranging from 3.4 to 7.8 (4,19). In addition, the ability of fluoroquinolones to promote PA resistant strains was also comparable with previous reports (3,4,19-21), although, a recent study has shown a clear divergence in the role of fluoroquinolones in PA resistance (22).

Our study also demonstrated that ertapenem could increase the likelihood of developing polyclonal and clonal MDR PA intestinal colonization. There are lingering concerns that extensive ertapenem use may compromise the susceptibility of PA to group 2 carbapenems. PA is considered to have inherent resistance to ertapenem, and its clinical use was expected to delay the emergence of carbapenem resistance. Previous studies (23,24) have concluded that, although ertapenem can select in vitro carbapenem resistance in PA, this phenomenon only occurs briefly in vivo. In fact, several studies suggest that ertapenem is not associated with increased carbapenem resistance in PA (25,26); however, these reports drew their conclusions from ecological analyses. Other studies have examined the effect of introducing ertapenem into a hospital on the susceptibility of PA to group 2 carbapenems (27,28); in these studies, the authors suspect that the improved susceptibility of PA to group 2 carbapenems was related to decreased fluoroquinolone use. However, in line with our finding, a recent patient-centered analysis, provided a possible
association of ertapenem with the appearance of PA resistance patterns (9).

This could be explained through collateral damage on the indigenous microflora, with its high capacity to kill significant numbers of normal gastrointestinal flora, promoting an ecological pressure for the spread of MDR PA; another possibility is that substantial and prolonged ertapenem use in the past could selectively promote the development of resistance mechanisms in PA.

We found a trend toward reduced risks of clonal MDR-non-XDR PA versus polyclonal MDR-non-XDR intestinal PA colonization with piperacillin-tazobactam. These data suggests that piperacillin-tazobactam was more selection neutral that other agents, and may result in the selection of fewer resistant PA strains.

There were several limitations in our study. The data set on which we performed our analysis was limited by the small number of patients colonized by different PA phenotypes. Although the conclusions are statistically significant, we recommend confirmation of our findings in larger epidemiological studies. In addition, restricting screening to stool samples might have resulted in an underestimation of early colonization with clonal MDR PA strains. For example, the possibility that clonal MDR PA strains were already present at other gut sites, cannot be excluded. Future studies that include multiple screening sites would help. Finally, the results may have been influenced by local epidemiological variables not applicable to other settings, including a relative high rate of horizontal transmission and almost universal antibiotic exposure.

On balance, we believe that this was a useful approach for the epidemiological evaluation of MDR PA, even XDR PA.
In conclusion, our study contributes to a better understanding of the dynamics of endogenous PA colonization. The molecular data alerted us to the fact that different clusters of MDR PA coexist in our ICU, although few of those evolve in the same patient. Additionally, the risk of acquiring MDR PA colonization varied between antibiotics classes; group 2 carbapenems and fluoroquinolones had established associations, while ertapenem may also have contributed to promoting MDR PA strains. On the other hand, piperacillin-tazobactam appeared to be less selective for the development of MDR PA. It is possible that using such a very broad-spectrum antibiotic might offer a valuable strategy to minimize the spread of MDR strains.
ACKNOWLEDGMENTS

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REFERENCES


FIG 1 Study schematic of the number of patients: phenotype and genotype of *Pseudomonas aeruginosa* colonization episodes during the 18-month study period.

a 10 MDR-non-XDR isolates and non-MDR isolates genotype relatedness

b UR clone: unrelated clone

c OP clone: overexpressing MexXY-OprM (reference 17);

d endemic clone (reference 5).

FIG 2 Probability of *Pseudomonas aeruginosa* digestive tract colonization. Solid line, non-MDR PA colonization; point-line, MDR-non-XDR PA colonization; point, XDR PA colonization.
<table>
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<tr>
<th></th>
<th>ICU admission PA intestinal colonization n=112 (%)</th>
<th>ICU admission PA non intestinal colonization n=302 (%)</th>
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<td>Age (mean ± SD, years)</td>
<td>65.3±13.3</td>
<td>62.2±14.3</td>
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<tr>
<td>Sex male</td>
<td>78 (69)</td>
<td>186 (61)</td>
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<td>Prior hospital stay</td>
<td>74 (66)</td>
<td>136 (45)</td>
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<td>Days of prior hospital stay (median, IQR)</td>
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<td>Charlson index (mean ± SD)</td>
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<td>20 (18)</td>
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<td>7 (6)</td>
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<td>4 (4)</td>
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<td>0.41</td>
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<td>Glycopeptides</td>
<td>11 (10)</td>
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<td>Total days prior antibiotics (median, IQR)</td>
<td>9 (2-22)</td>
<td>10.5 (4-21)</td>
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*a IQR, interquartile range
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<td>PT (18)</td>
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<td>CARB-2 (1) MDR-non-XDR/OP clone</td>
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<td>8</td>
<td>NAP (3)</td>
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<td>AG (4) PT (8) GLYC (3) MDR-non-XDR/OP clone</td>
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(*) non-MDR and MDR isolate in the same sample. APCEF: antipseudomonal cephalosporins; PT, Piperacillin-tazobactam; FQ, Fluoroquinolones; AG, Aminoglycosides; NAP, Non antipseudomonal penicillins; NACEF, Non antipseudomonal cephalosporins; COL, Colistin; CARB-1, Group 1 Carbapenem; CARB-2, Group 2 Carbapenem; GLYC, Glycopeptides
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<tr>
<th>Characteristic</th>
<th>Crude Analysis</th>
<th>Adjusted analysis</th>
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<tbody>
<tr>
<td></td>
<td>cHR (95%CI)</td>
<td>p</td>
</tr>
<tr>
<td>Age &gt;65y</td>
<td>1.11 (0.72-1.73)</td>
<td>0.63</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.20 (0.94-1.52)</td>
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</tr>
<tr>
<td>SAPS score ICU admission (&gt;40)</td>
<td>1.53 (0.79-2.37)</td>
<td>0.054</td>
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<tr>
<td>Charlson index ≥ 3</td>
<td>1.96 (1.26-3.04)</td>
<td>0.003</td>
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<tr>
<td>Prior hospital stay</td>
<td>1.15 (0.75-1.78)</td>
<td>0.52</td>
</tr>
<tr>
<td>Prior Fluoroquinolones</td>
<td>1.02 (1.00-1.04)</td>
<td>0.013</td>
</tr>
<tr>
<td>Prior Aminoglycosides</td>
<td>1.02 (0.94-1.12)</td>
<td>0.59</td>
</tr>
<tr>
<td>Prior Carbapenems</td>
<td>1.04 (1.01-1.07)</td>
<td>0.007</td>
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<tr>
<td>Prior Ertapenems</td>
<td>1.08 (1.03-1.14)</td>
<td>0.002</td>
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<tr>
<td>Prior Colistin</td>
<td>1.03 (0.99-1.07)</td>
<td>0.11</td>
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<td>Prior antipseudomonal Cefalosporins</td>
<td>1.01 (0.98-1.05)</td>
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<td>Prior other Cefalosporins</td>
<td>1.00 (0.98-1.03)</td>
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<tr>
<td>Prior Piperacillin-Tazobactam</td>
<td>0.98 (0.94-1.00)</td>
<td>0.13</td>
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<tr>
<td>Prior Penicillins</td>
<td>1.00 (0.99-1.02)</td>
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<tr>
<td>Prior Glycopeptids</td>
<td>0.99 (0.97-1.01)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

* Antibiotics per day
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Crude Analysis</th>
<th>Adjusted analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cHR (95%CI)</td>
<td>p</td>
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<tr>
<td>Age &gt;65y</td>
<td>0.77 (0.33-1.80)</td>
<td>0.55</td>
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<tr>
<td>Male gender</td>
<td>1.90 (0.74-4.87)</td>
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<td>SAPS score ICU admission (&gt;40)</td>
<td>1.23 (0.53-2.87)</td>
<td>0.62</td>
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<tr>
<td>Charlson index ≥ 3</td>
<td>2.48 (1.01-6.11)</td>
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<td>Prior hospital stay</td>
<td>0.75 (0.33-1.68)</td>
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<tr>
<td>Prior non-MDR colonization</td>
<td>0.43 (0.17-1.09)</td>
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<tr>
<td>Prior Fluoroquinolones(^a)</td>
<td>1.05 (0.96-1.16)</td>
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<tr>
<td>Prior Aminoglycosides(^a)</td>
<td>114 (0.79-1.64)</td>
<td>0.46</td>
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<td>Prior Carbapenems(^a)</td>
<td>0.94 (0.84-1.04)</td>
<td>0.23</td>
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<tr>
<td>Prior Ertapenem(^a)</td>
<td>1.07 (1.00-1.15)</td>
<td>0.048</td>
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<tr>
<td>Prior Colistin(^a)</td>
<td>0.96 (0.88-1.03)</td>
<td>0.24</td>
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<tr>
<td>Prior antipseudomonal Cefalosporins(^a)</td>
<td>0.96 (0.88-1.05)</td>
<td>0.38</td>
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<td>Prior other Cefalosporins(^a)</td>
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<td>0.95</td>
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<tr>
<td>Prior Piperacillin-Tazobactam(^a)</td>
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<td>Prior Penicillin(^a)</td>
<td>1.27 (0.57-2.84)</td>
<td>0.56</td>
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<tr>
<td>Prior Glycopeptids(^a)</td>
<td>0.96 (0.89-1.03)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

\(^a\) Antibiotics per day